tetrahydrobiopterin deficiency

Tetrahydrobiopterin deficiency is a rare disorder characterized by a shortage (deficiency) of a molecule called tetrahydrobiopterin or BH4. This condition alters the levels of several substances in the body, including phenylalanine. Phenylalanine is a building block of proteins (an amino acid) that is obtained through the diet. It is found in foods that contain protein and in some artificial sweeteners. High levels of phenylalanine are present from early infancy in people with untreated tetrahydrobiopterin deficiency. This condition also alters the levels of chemicals called neurotransmitters, which transmit signals between nerve cells in the brain.

Infants with tetrahydrobiopterin deficiency appear normal at birth, but medical problems ranging from mild to severe become apparent over time. Signs and symptoms of this condition can include intellectual disability, progressive problems with development, movement disorders, difficulty swallowing, seizures, behavioral problems, and an inability to control body temperature.

Frequency

This condition is rare, affecting an estimated 1 in 500,000 to 1 in 1 million newborns. In most parts of the world, tetrahydrobiopterin deficiency accounts for 1 to 3 percent of all cases of elevated phenylalanine levels. The remaining cases are caused by a similar condition called phenylketonuria (PKU). In certain countries, including Saudi Arabia, Taiwan, China, and Turkey, it is more common for elevated levels of phenylalanine to be caused by tetrahydrobiopterin deficiency than by PKU.

Genetic Changes

Tetrahydrobiopterin deficiency can be caused by mutations in one of several genes, including *GCH1*, *PCBD1*, *PTS*, and *QDPR*. These genes provide instructions for making enzymes that help produce and recycle tetrahydrobiopterin in the body. Tetrahydrobiopterin normally helps process several amino acids, including phenylalanine. It is also involved in the production of neurotransmitters.

If one of the enzymes fails to function correctly because of a gene mutation, little or no tetrahydrobiopterin is available to help process phenylalanine. As a result, phenylalanine can build up in the blood and other tissues. Because nerve cells in the brain are particularly sensitive to phenylalanine levels, excessive amounts of this substance can cause brain damage. Tetrahydrobiopterin deficiency can also alter the levels of certain neurotransmitters, which disrupts normal brain function. These abnormalities underlie the intellectual disability and other characteristic features of the condition.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- BH4 deficiency
- hyperphenylalaninemia caused by a defect in biopterin metabolism
- hyperphenylalaninemia, non-phenylketonuric
- non-phenylketonuric hyperphenylalaninemia

Diagnosis & Management

Formal Diagnostic Criteria

- ACT Sheet: Increased phenylalanine
  https://www.ncbi.nlm.nih.gov/books/NBK55827/bin/Phenylalanine.pdf

Genetic Testing

- Genetic Testing Registry: 6-pyruvoyl-tetrahydropterin synthase deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0878676/
- Genetic Testing Registry: Dihydropteridine reductase deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268465/
- Genetic Testing Registry: GTP cyclohydrolase I deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268467/
- Genetic Testing Registry: Hyperphenylalaninemia, BH4-deficient, D
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1849700/

Other Diagnosis and Management Resources

- Baby's First Test: Biopterin Defect in Cofactor Biosynthesis
  http://www.babysfirsttest.org/newborn-screening/conditions/biopterin-defect-in-cofactor-biosynthesis
- Baby's First Test: Biopterin Defect in Cofactor Regeneration
  http://www.babysfirsttest.org/newborn-screening/conditions/biopterin-defect-in-cofactor-regeneration
- MedlinePlus Encyclopedia: Serum Phenylalanine Screening
  https://medlineplus.gov/ency/article/003362.htm

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Serum Phenylalanine Screening
  https://medlineplus.gov/ency/article/003362.htm
- Health Topic: Newborn Screening
  https://medlineplus.gov/newbornscreening.html
- Health Topic: Phenylketonuria
  https://medlineplus.gov/phenylketonuria.html

Genetic and Rare Diseases Information Center

- Tetrahydrobiopterin deficiency
  https://rarediseases.info.nih.gov/diseases/7751/tetrahydrobiopterin-deficiency

Educational Resources

- Children Living with Inherited Metabolic Diseases (CLIMB) (UK): Tetrahydrobiopterin Deficiency
  http://www.climb.org.uk/IMD/Tango/TetrahydrobiopterinDeficiency-General.pdf
- Disease InfoSearch: Tetrahydrobiopterin deficiency
  http://www.diseaseinfosearch.org/Tetrahydrobiopterin+deficiency/7038
- MalaCards: tetrahydrobiopterin deficiency
  http://www.malacards.org/card/tetrahydrobiopterin_deficiency
- Orphanet: 6-pyruvoyl-tetrahydropterin synthase deficiency
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=13
- Orphanet: Dehydratase deficiency
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=1578

- Orphanet: Dihydropteridine reductase deficiency
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=226
- Orphanet: GTP cyclohydrolase I deficiency
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=2102

Patient Support and Advocacy Resources

- Children Living with Inherited Metabolic Diseases (CLIMB) (UK)
  http://www.climb.org.uk/
- National Organization for Rare Disorders
  https://rarediseases.org/rare-diseases/tetrahydrobiopterin-deficiency/

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22tetrahydrobiopterin+deficiency%22+OR+%22phenylketonurias%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28tetrahydrobiopterin+deficiency%5BTIAB%5D%29+OR+%28bh4+deficiency%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

OMIM

- HYPERPHENYLALANINEMIA, BH4-DEFICIENT, A
  http://omim.org/entry/261640
- HYPERPHENYLALANINEMIA, BH4-DEFICIENT, B
  http://omim.org/entry/233910
- HYPERPHENYLALANINEMIA, BH4-DEFICIENT, C
  http://omim.org/entry/261630
- HYPERPHENYLALANINEMIA, BH4-DEFICIENT, D
  http://omim.org/entry/264070

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